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(57) Abstract

This invention relates to a family of diacyl benzimidazole analogs, which are inhibitors of the IgE response to allergens. These compounds are useful in the treatment of allergy and/or asthma or any diseases where IgE is pathogenic.

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BENZIMIDAZOLE DERIVATIVES AS MODULATORS OF IgE

Background of the Invention

This invention relates to small molecule inhibitors of the IgE response to allergens that are useful in the treatment of allergy and/or asthma or any diseases where IgE is pathogenic.

An estimated 10 million persons in the United States have asthma, about 5% of the population. The estimated cost of asthma in the United States exceeds \$6 billion. About 25% of patients with asthma who seek emergency care require hospitalization, and the largest single direct medical expenditure for asthma has been inpatient hospital services (emergency care), at a cost of greater than \$1.6 billion. The cost for prescription medications, which increased 54% between 1985 and 1990, was close behind at \$1.1 billion (Kelly, *Pharmacotherapy* 12:13S-21S (1997)).

According to the National Ambulatory Medical Care Survey, asthma accounts for 1% of all ambulatory care visits, and the disease continues to be a significant cause of missed school days in children. Despite improved understanding of the disease process and better drugs, asthma morbidity and mortality continue to rise in this country and worldwide (U.S. Department of Health and Human Services; 1991, publication no. 91-3042). Thus, asthma constitutes a significant public health problem.

The pathophysiologic processes that attend the onset of an asthmatic episode can be broken down into essentially two phases, both marked by bronchoconstriction, that causes wheezing, chest tightness, and dyspnea. The first, early phase asthmatic response is triggered by allergens, irritants, or exercise. Allergens cross-link immunoglobulin E (IgE) molecules bound to receptors on mast cells, causing them to release a number of pre-formed inflammatory mediators, including histamine. Additional triggers include the osmotic changes in airway tissues following exercise or the inhalation of cold, dry air. The second, late phase response that follows is characterized by infiltration of activated eosinophils and other inflammatory cells into airway tissues, epithelial desquamonon, and by the presence of highly viscous mucus within the airways. The damage caused by this inflammatory response leaves the airways "primed" or sensitized, such that smaller triggers are required to elicit subsequent asthma symptoms.

A number of drugs are available for the palliative treatment of asthma; however, their efficacies vary markedly. Short-acting β_2 -adrenergic agonists, terbutaline and albuterol, long the mainstay of asthma treatment, act primarily during the early phase as bronchodilators. The newer

long-acting β_2 -agonists, salmeterol and formoterol, may reduce the bronchoconstrictive component of the late response. However, because the β_2 -agonists do not possess significant antiinflammatory activity, they have no effect on bronchial hyperreactivity.

Numerous other drugs target specific aspects of the early or late asthmatic responses. For example, antihistamines, like loratadine, inhibit early histamine-mediated inflammatory responses. Some of the newer antihistamines, such as azelastine and ketotifen, may have both antiinflammatory and weak bronchodilatory effects, but they currently do not have any established efficacy in asthma treatment. Phosphodiesterase inhibitors, like theophylline/xanthines, may attenuate late inflammatory responses, but there is no evidence that these compounds decrease bronchial hyperreactivity. Anticholinergics, like ipratopium bromide, which are used in cases of acute asthma to inhibit severe bronchoconstriction, have no effect on early or late phase inflammation, no effect on bronchial hyperreactivity, and therefore, essentially no role in chronic therapy.

The corticosteroid drugs, like budesonide, are the most potent antiinflammatory agents. Inflammatory mediator release inhibitors, like cromolyn and nedocromil, act by stabilizing mast cells and thereby inhibiting the late phase inflammatory response to allergen. Thus, cromolyn and nedocromil, as well as the corticosteroids, all reduce bronchial hyperreactivity by minimizing the sensitizing effect of inflammatory damage to the airways. Unfortunately, these antiinflammatory agents do not produce bronchodilation.

Several new agents are currently being developed that inhibit specific aspects of asthmatic inflammation. For instance, leukotriene receptor antagonists (ICI-204, 219, accolate), specifically inhibit leukotriene-mediated actions. The leukotrienes have been implicated in the production of both airway inflammation and bronchoconstriction.

Thus, while numerous drugs are currently available for the treatment of asthma, these compounds are primarily palliative and/or have significant side effects. Consequently, new therapeutic approaches which target the underlying cause rather than the cascade of symptoms would be highly desirable. Asthma and allergy share a common dependence on IgE-mediated events. Indeed, it is known that excess IgE production is the underlying cause of allergies in general and allergic asthma in particular (Duplantier and Cheng, *Ann. Rep. Med. Chem.* 29:73-81 (1994)). Thus, compounds that lower IgE levels may be effective in treating the underlying cause of asthma and allergy.

None of the current therapies eliminate the excess circulating IgE. The hypothesis that lowering plasma IgE may reduce the allergic response, was confirmed by recent clinical results with chimeric anti-IgE antibody, CGP-51901, and recombinant humanized monoclonal antibody, rhuMAB-E25. Indeed, three companies, Tanox Biosystems, Inc., Genentech Inc. and Novartis AG are collaborating in the development of a humanized anti-IgE antibody (BioWorld® Today, February 26, 1997, p. 2) which will treat allergy and asthma by neutralizing excess IgE. Tanox has already successfully tested the anti-IgE antibody, CGP-51901, which reduced the severity and duration of nasal symptoms of allergic rhinitis in a 155-patient Phase II trial (Scrip #2080, Nov 24, 1995, p.26). Genentech recently disclosed positive results from a 536 patient phase-II/III trials of its recombinant humanized monoclonal antibody, rhuMAB-E25 (BioWorld® Today, November 10, 1998, p. 1). The antibody, rhuMAB-E25, administered by injection (highest dose 300 mg every 2 to 4 weeks as needed) provided a 50% reduction in the number of days a patient required additional "rescue" medicines (antihistimines and decongestants), compared to placebo. An NDA filing for this product is projected to be in the year 2000. The positive results from anti-IgE antibody trials suggest that therapeutic strategies aimed at IgE down-regulation may be effective.

Summary of the Invention

The present invention discloses a family of related compounds for use in the treatment of a condition associated with an excess IgE level. The benzimidazole inhibitors of IgE in accordance with the present invention are represented by the generic formula:

X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF₃, OCF₃, CONH₂, CONHR and NHCOR₁. R is selected from the group consisting of H, CH₃, C₂H₅, C₃H₇, C₄H₉,

CH₂Ph, and CH₂C₆H₄-F(p-). R₁ and R₂ are independently selected from the group consisting of H, aryl, substituted aryl, cycloaryl substituted cycloaryl, multi-ring cycloaryl, benzyl, substituted benzyl and the like. Substitutions are alkyl, aryl, CF3, CH3, OCH₃, OH, CN, COOR, COOH and the like.

In accordance with another aspect of the invention, there is disclosed a composition for use in the treatment of an allergic condition comprising the diacyl benzimidazole inhibitor of IgE disclosed above and at least one additional active ingredient, combined in a pharmaceutically acceptable diluent. The additional active ingredients may be selected from the group consisting of short-acting β_2 -adrenergic agonists, like terbutaline and albuterol, long-acting β_2 -adrenergic agonists, like salmeterol and formoterol, antihistamines, like loratedine, azelastine and ketotifen, phosphodiesterase inhibitors, anticholinergic agents, corticosteroids, inflammatory mediator release inhibitors and leukotriene receptor antagonists.

In accordance with another aspect of the invention, there is disclosed a family of symmetric and asymmetric diacyl and monoacyl benzimidazole compounds for use in the treatment of an allergic condition comprising the following species:

Structure	BIAA
0,000	C ₂₇ H ₂₀ N ₄ O ₂
	CLOGP
	5.47

Structure	BIAB
0,00000	C ₂₇ H ₁₉ CIN ₄ O ₂
	CLOGP
	6.24

Structure	BIAC
arapio"	C ₂₈ H ₂₂ N ₄ O ₃
	CLOGP
	5.58

Structure	BIAD
0,000	C ₂₆ H ₁₉ N ₅ O ₂
"-"	CLOGP
	4.28

Structure	BIAE
growni.	C ₃₀ H ₂₆ N ₄ O ₅
° 'i	CLOGP
·	4.82

Structure	BIAF
Oroginis	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂
	CLOGP
	6.97

Structure	BIAG
Quano p	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂
"	CLOGP
	5.31

Structure	BIAH
0,000000	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂
"-"	CLOGP
•	6.14

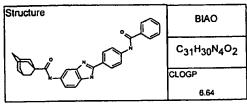
Structure	BIAI
04.04.0	C ₂₇ H ₂₆ N ₄ O ₂
*	CLOGP
	6.01

Structure	BIAJ
0,000	C ₂₆ H ₂₄ N ₄ O ₂
	CLOGP
	5.45

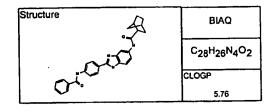
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O'COTO	C ₂₅ H ₁₈ N ₄ O ₂ S
-	CLOGP
	5.20

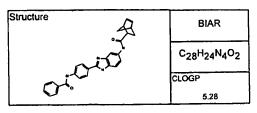
Structure	BIAM
٥٠٠٠٥	C ₃₀ H ₂₄ N ₄ O ₂
	CLOGP
	5.74

Structure	BIAN
010175°	C ₂₂ H ₁₈ N ₄ O ₂
***	CLOGP
	3.98



Structure	BIAP
0,000	C ₂₈ H ₂₈ N ₄ O ₂
	CLOGP
	6.57





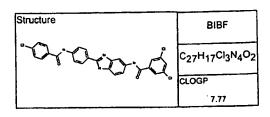
Structure	BIBA
Orono	C ₂₇ H ₁₉ CIN ₄ O ₂
*	CLOGP
	6.26

Structure	BIBB
orano.	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂
	CLOGP.
	7.04

Structure	BIBC
000000°	C ₂₈ H ₂₁ CIN ₄ O ₃
	CLOGP
	6.38

Structure	BIBD
000000	C ₂₆ H ₁₈ CIN ₅ O ₂
	CLOGP
	5.08

Structure	BIBE
araiori.	C ₃₀ H ₂₅ CIN ₄ O ₅
,	CLOGP
	5.62



Structure	BIBG
C107070	C ₂₇ H ₁₇ Cl ₃ N ₄ O ₂
	CLOGP
	6.11

Structure	ВІВН
orano.	C ₂₇ H ₁₇ Cl ₃ N ₄ O ₂
	CLOGP
	6.94

Structure	BIBI
Oranio	C ₂₇ H ₂₅ CIN ₄ O ₂
	CLOGP
	6.81

Structure	BIBJ
Of Ording	C ₂₆ H ₂₃ CIN ₄ O ₂
N-1	CLOGP
	6.25

Structure	BIBK
O'TOTO	C ₂₅ H ₁₇ CIN ₄ O ₂ S
•	CLOGP
	6.00

Structure	BIBL
0,0000	C ₂₅ H ₁₇ CIN ₄ O ₂ S
	CLOGP
	6.00

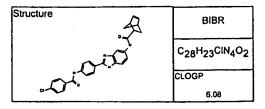
Structure	вівм
المحريب المحادث	C ₃₀ H ₂₃ CIN ₄ O ₂
	CLOGP
	6.54

Structure	BIBN
"Of" Of" >.	C ₂₂ H ₁₇ CIN ₄ O ₂
	CLOGP
	4.78

Structure	BIBO
R. OT	C31H29CIN4O2
	CLOGP
	7.43

Structure	BIBP
Orano O	C ₂₈ H ₂₇ CIN ₄ O ₂
	CLOGP
	7.37

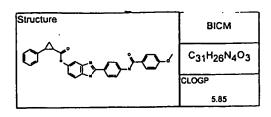
Structure	A.	BIBQ
~		C ₂₈ H ₂₅ CIN ₄ O ₂
المنتجم	-	CLOGP
		6.56



5.32

Structure	BICA	Structure	вісв
Orano O	C ₂₈ H ₂₂ N ₄ O ₃	·Orano	C ₂₈ H ₂₁ CIN ₄ O ₃
	CLOGP		CLOGP .
	5.58		6.35
	<u> </u>		
Structure	BICC	Structure	BICD
orano.	C ₂₉ H ₂₄ N ₄ O ₄	O'COIN'S	C ₂₇ H ₂₁ N ₅ O ₃
	CLOGP		CLOGP
	5.70		4.39
Structure	BICE	Structure	BICF
0,0000	C ₃₁ H ₂₈ N ₄ O ₆	10,000.0	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃
,	CLOGP		CLOGP
	4.93		7.09
Structure	BICG	Structure	вісн
Structure °°C', 'S	BICG C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃	Structure	BICH C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃
Structure		Structure	
Structure	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃	Structure	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃
Structure	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃	Structure	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃
Structure **Chings Structure	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃	Structure	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃
النيام، م	CLOGP 5.43	٥٠٥٠٥٠	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃ CLOGP 6.26
النيام، م	CLOGP 5.43	٥٠٥٠٥٠	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃ CLOGP 6.26
النيام، م	CLOGP 5.43 BICI C28H28N4O3	٥٠٥٠٥٠	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃ CLOGP 6.26 BICJ C ₂₇ H ₂₆ N ₄ O ₃
النيام، م	CLOGP C28H20Cl2N4O3 CLOGP 5.43 BICI C28H28N4O3 CLOGP	Structure "Change"	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃ CLOGP 6.26 BICJ C ₂₇ H ₂₆ N ₄ O ₃ CLOGP
النيام، م	CLOGP C28H20Cl2N4O3 CLOGP 5.43 BICI C28H28N4O3 CLOGP	٥٠٥٠٥٠	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃ CLOGP 6.26 BICJ C ₂₇ H ₂₆ N ₄ O ₃ CLOGP
Structure	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃ CLOGP 5.43 BICI C ₂₈ H ₂₈ N ₄ O ₃ CLOGP 6.12	Structure "Change"	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃ CLOGP 6.26 BICJ C ₂₇ H ₂₆ N ₄ O ₃ CLOGP 5.56

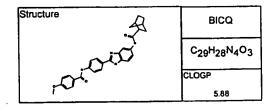
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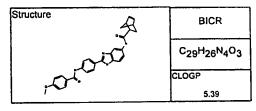


Structure	BICN
of Other.	C ₂₃ H ₂₀ N ₄ O ₃
"-	CLOGP
	4.09

Structure	BICO
	C ₃₂ H ₃₂ N ₄ O ₃
	CLOGP
	6.75

Structure	BICP
Orano O	C ₂₉ H ₃₀ N ₄ O ₃
	CLOGP
	6.68





Structure	BIDA
0,0,0	C ₂₆ H ₁₉ N ₅ O ₂
	CLOGP
	4.60

Structure	BIDB
Oranio.	C ₂₆ H ₁₈ CIN ₅ O ₂
	CLOGP
	5.37

Structure	BIDC
0,000	C ₂₇ H ₂₁ N ₅ O ₃
	CLOGP
	4.71

Structure	BIDD
0,00,0	C ₂₅ H ₁₈ N ₆ O ₂
	CLOGP
	3.41

Structure	BIDE
Growns.	C ₂₉ H ₂₅ N ₅ O ₅
7	CLOGP
	3.95

Structure	BIDG	Structure	BIDH
Cinoro	C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂	٠٥٠٥٠٥٠	C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂
	CLOGP 4.44		CLOGP 5.27
Charatura		Structure	
Structure	BIDI	Siluciore	BIDJ
10,00000	C ₂₆ H ₂₅ N ₅ O ₂	O'O'O'	C ₂₅ H ₂₃ N ₅ O ₂
	5.14		4.58
Structure	BIDK	Structure	BIDL
0,000	C ₂₄ H ₁₇ N ₅ O ₂ S	Oromic	C ₂₄ H ₁₇ N ₅ O ₂ S
	CLOGP 4.33		CLOGP 4.33
	1		<u> </u>
Structure	ВІДМ	Structure	BIDN
	C ₂₉ H ₂₃ N ₅ O ₂		C ₂₁ H ₁₇ N ₅ O ₂
	CLOGP 4.87		3.11
Structure	BIDO	Structure	BIDP
	C ₃₀ H ₂₉ N ₅ O ₂	10,000	C ₂₇ H ₂₇ N ₅ O ₂
	CLOGP 5.77		CLOGP 5.70
	4.77		
Structure	BIDQ	Structure	BIDR
P. Oin	C ₂₇ H ₂₅ N ₅ O ₂	Structure	C ₂₇ H ₂₃ N ₅ O ₂
"J."	CLOGP 4.89		CLOGP 4.41

BIEB

C30H25CIN4O5

5.59

BIED

 $C_{29}H_{25}N_5O_5$

3.63

BIEF

C₃₀H₂₄Cl₂N₄O₅

6.32

BIEH

C₃₀H₂₄Cl₂N₄O₅

5.49

4.80 ·

CLOGP

CLOGP

CLOGP

CLOGP

Structure	BIEA	Structure
~ 9	5.5	~ 0
12.	C ₃₀ H ₂₆ N ₄ O ₅	1° Diració
1.77	CLOGP	1 , , , , ,
	4.82	
	4.02	
		<u> </u>
Structure	BIEC	Structure
1 -9		الله الله
1. D. C	C ₃₁ H ₂₈ N ₄ O ₆	Mon
1 8 2 1 2	CLOGP	
	4.93	
		Structure
Structure	BIEE	
1.2	G 11 N O	100
	C ₃₃ H ₃₂ N ₄ O ₈	I was printing
	CLOGP	
	4.17	
Structure	2150	Structure
	BIEG	- 0
1	C ₃₀ H ₂₄ Cl ₂ N ₄ O ₅	1.2. ·
	CLOGP	
	4.66	

BIEI

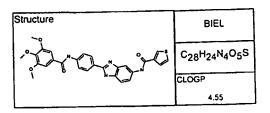
C30H32N4O5

CLOGP

Structure	BIEJ
Drango	C ₂₉ H ₃₀ N ₄ O ₅
	CLOGP

Structure	BIEK
Dra- 30	C ₂₈ H ₂₄ N ₄ O ₅ S
1 , , , ,	CLOGP
	4,55

Structure

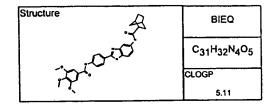


Structure	BIEM
المكريب بريادك	C ₃₃ H ₃₀ N ₄ O ₅
\	CLOGP
	5.09

Structure	BIEN
· 10 - 10 - 10 - 10 - 10 - 10 - 10 - 10	C ₂₅ H ₂₄ N ₄ O ₅
	CLOGP
	3.33

Structure	ئہا	BIEO
		C ₃₄ H ₃₆ N ₄ O ₅
		CLOGP
		5.99

Structure	BIEP
O'como	C ₃₁ H ₃₄ N ₄ O ₅
	CLOGP
	5.92



Structure	Ŗ.	BIER
1	کنتر ,	C ₃₁ H ₃₀ N ₄ O ₅
,,,,		CLOGP
, ,		4.63

Structure	BIFA
	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂
	CLOGP
	7.00

Structure ·	BIFB
\$ 0. D.	C ₂₇ H ₁₇ Cl ₃ N ₄ O ₂
	CLOGP
	7.78

Structure	BIFC
Drango'	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃
	CLOGP
	7.12

Structure	BIFD
2000	C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂
	CLOGP
	5.82

Structure	BIFE
Drawis.	C ₃₀ H ₂₄ Cl ₂ N ₄ O ₅
	CLOGP
	6.35

Structure	BIFG	Structure	BIFH
المناب المالية	27H16CI4N4O2	Drawio.	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂
C	LOGP 6.85		CLOGP 7.68
Structure	BIFI	Structure	BIFJ
Draw of	27H24Cl2N4O2	D'Ornio	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₂
	LOGP 7.54	h-0-1	CLOGP 6.99
			•
Structure	BIFK	Structure	BIFL
	25H ₁₆ Cl ₂ N ₄ O ₂	Dra vi	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ s
	CLOGP		CLOGP
	6.74		6.74
Structure		Structure	BIFN
	BIFM	2	
	C ₃₀ H ₂₂ Cl ₂ N ₄ O ₂	of the state of th	C ₂₂ H ₁₆ Cl ₂ N ₄ O ₂
	7.28		CLOGP 5.51
L			
Structure	BIFO	Structure	BIFP
	C ₃₁ H ₂₈ Cl ₂ N ₄ O ₂	Oin Ora	C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂
	CLOGP 8.17	***************************************	CLOGP 8.10
L			
Structure	BIFQ	Structure	BIFR
Structure	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₂	(Disc.	C ₂₈ H ₂₂ Cl ₂ N ₄ O ₂
		, , , ~	CLOGP

Structure	BIGA
	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂
	CLOGP
	5.34
Structure	BIGC
~	

١	Structure	BIGB
	~	C ₂₇ H ₁₇ Cl ₃ N ₄ O ₂
		CLOGP
		6.12

Structure	BIGC
Granio"	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃
a N-1	CLOGP
	5.46

Structure	BIGD
O'CONO	C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂
	CLOGP
	4.16

Structure	BIGE
Good.	C ₃₀ H ₂₄ Cl ₂ N ₄ O ₅
	CLOGP
	4.69

Structure	BIGF
Groming.	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂
	CLOGP
•	6.85

Structure	BIGG
Ciron D	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂
	CLOGP
	5.19

Structure	BIGH
Ganib.	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂
	CLOGP
	6.02

Structure	BIGI
G'anio	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂
	CLOGP
	5.88

Structure	BIGJ
Grond O	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₂
" "	CLOGP
	5.33

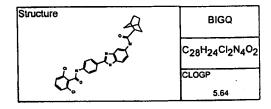
Structure	BIGK
Grapin Dir	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S
	CLOGP
	5.08

Structure	BIGM
المناب المالية	C ₃₀ H ₂₂ Cl ₂ N ₄ O ₂
, , , , , , , , , , , , , , , , , , ,	CLOGP
	5.62

Structure	BIGN
G'O.	C ₂₂ H ₁₆ Cl ₂ N ₄ O ₂
	CLOGP
	3.85

Structure	. ")	BIGO
		C31H28Cl2N4O2
	•	CLOGP
	<u>.</u>	6.51

Structure	BIGP
G'anio	C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂
	CLOGP
	6.44



Structure	A	BIGR
		C ₂₈ H ₂₂ Cl ₂ N ₄ O ₂
مهتريم	, -	CLOGP
₩ .		5.16

Structure	BIHA
Orono O	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂
*-	CLOGP
	6.17

Structure	вінв
"Oragony"	C ₂₇ H ₁₇ Cl ₃ N ₄ O ₂
	CLOGP
	6.95

Structure	вінс
growno'	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃
	CLOGP
	6.29

Structure	BIHD
047079	C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂
	CLOGP
	4.99

Structure	BIHE
grang.	C ₃₀ H ₂₄ Cl ₂ N ₄ O ₅
	CLOGP
	5.52

Structure	вінс	Structure	вінн
Circon C	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂	"Pranio	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂
	CLOGP		CLOGP
	6.02		6.85
			}
Structure	віні	Structure	ВІНЈ
010170	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂	Of Org	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₂
	CLOGP		CLOGP
	6.71		6.16
Structure		Structure	D# "
I 0. / 5	ВІНК		BIHL
1 Com	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ s	LA COLD	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S
	CLOGP		CLOGP
	5.91		5.91
Structure	DUM	Structure	BIHN
	ВІНМ	0	
I		1 11 1 11 11 11 11 11	
المناب المناب	C ₃₀ H ₂₂ Cl ₂ N ₄ O ₂	ALDED.	C ₂₂ H ₁₆ Cl ₂ N ₄ O ₂
٠٥٠٥٠٥٠	CLOGP	A. Chior.	CLOGP
٠٥٠٥٠٥٠			
Structure	6.45	Structure	CLOGP 4.68
	6.45	Structure	4.68
	6.45	Structure "Company"	BIHP C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂
	BIHO C ₃₁ H ₂₈ Cl ₂ N ₄ O ₂ CLOGP	Structure """ "" "" "" "" "" "" "" ""	BIHP C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂ CLOGP
	BIHO C ₃₁ H ₂₈ Cl ₂ N ₄ O ₂	Structure """ "" "" "" "" "" "" "" ""	BIHP C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂
Structure	BIHO C ₃₁ H ₂₈ Cl ₂ N ₄ O ₂ CLOGP	oraror?	BIHP C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂ CLOGP
Structure	BIHO C ₃₁ H ₂₈ Cl ₂ N ₄ O ₂ CLOGP 7.34 BIHQ	oraror?	BIHP C28H26Cl2N4O2 CLOGP 7.27
Structure	BIHO C ₃₁ H ₂₈ Cl ₂ N ₄ O ₂ CLOGP 7.34	oforor?	BIHP C28H26Cl2N4O2 CLOGP 7.27

Structure	BIKA
01000	C ₂₅ H ₁₈ N ₄ O ₂ S
	CLOGP
	5.20

Structure	ВІКВ
0,00000.	C ₂₅ H ₁₇ CIN ₄ O ₂ S
	CLOGP
	5.98

Structure	вікс
000000	C ₂₆ H ₂₀ N ₄ O ₃ S
	CLOGP
	5.32

Structure	BIKD
0,000	C ₂₄ H ₁₇ N ₅ O ₂ S
	CLOGP
	4.02

Structure	BIKF
0,00000	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S CLOGP
	6.71

Structure	BIKG
Ciron of	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S
	CLOGP
	5.05

Structure	вікн
المرسين.	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S
	CLOGP
	5.88

Structure	BIKI
0,000	C ₂₅ H ₂₄ N ₄ O ₂ S
	CLOGP
	5.74

Structure	ВІКЈ
04.00.00	C ₂₄ H ₂₂ N ₄ O ₂ S
	CLOGP
	5.19

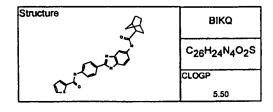
Structure	вікк
O'COTO	C ₂₃ H ₁₆ N ₄ O ₂ S ₂
	CLOGP
	4 04

Structure	BIKM
المرين	C ₂₈ H ₂₂ N ₄ O ₂ S
	CLOGP
	5.48

Structure	BIKN
	C ₂₀ H ₁₆ N ₄ O ₂ S
	CLOGP
	3.71

Structure	ВІКО
	C ₂₉ H ₂₈ N ₄ O ₂ S
	CLOGP
	6.37

Structure	BIKP
0,000	C ₂₆ H ₂₆ N ₄ O ₂ S
	CLOGP
	6.30



Structure	£.	BIKR
	.53 ·	C ₂₆ H ₂₂ N ₄ O ₂ S
مند ا	, -	CLOGP
L7 °		5.02

Structure	BILA
2000	C ₂₅ H ₁₈ N ₄ O ₂ S
	CLOGP
	5.20

Structure	BILB
900000°	C ₂₅ H ₁₇ CIN ₄ O ₂ S
	CLOGP
	5.98

Structure	BILC
12000°	C ₂₆ H ₂₀ N ₄ O ₃ S
	CLOGP ·
·	5.32

Structure	BILD
01000	C ₂₄ H ₁₇ N ₅ O ₂ S
	CLOGP
	4.02

Structure	BILE
2000	C ₂₈ H ₂₄ N ₄ O ₅ S
, ,	CLOGP
	4.55

Structure	BILG
Girror P	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ s
· · ·	CLOGP
	5.05

Structure	BILH
20000	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S
	CLOGP
	5.88

Structure	BILI
04000	C ₂₅ H ₂₄ N ₄ O ₂ S
	CLOGP
	5.74

Structure	BILJ
0,000	C ₂₄ H ₂₂ N ₄ O ₂ S
	CLOGP
	5.19

Structure	BILK
0,000	C ₂₃ H ₁₆ N ₄ O ₂ S ₂
•	CLOGP
	4.94

Structure	BILL
0000	C ₂₃ H ₁₆ N ₄ O ₂ S ₂
	CLOGP
	4.94

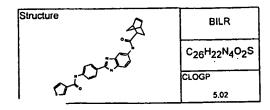
Structure	BILM
	C ₂₈ H ₂₂ N ₄ O ₂ S
	CLOGP
	5.48

Structure	BILN
	C ₂₀ H ₁₆ N ₄ O ₂ S
	CLOGP
	3.71

Structure	BILO
R. O	C ₂₉ H ₂₈ N ₄ O ₂ S
	CLOGP
	6.37

Structure	BILP
0,000	C ₂₆ H ₂₆ N ₄ O ₂ S
	CLOGP
	6.30

Structure	BILQ
کنہ	C ₂₆ H ₂₄ N ₄ O ₂ S
	CLOGP
(2).	5.50



Structure	BIJG
Q-10-70	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₂
	CLOGP
	5.29

Structure	ВІЈН
	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₂
*	CLOGP
·	6.12

Structure

Structure

C27H26N4O2

CLOGP

6.01

Structure	
~	BIIB
dediso.	C ₂₇ H ₂₅ CIN ₄ O ₂
	CLOGP
	6.78

Structure	BIIC
0,0000	C ₂₈ H ₂₈ N ₄ O ₃
	CLOGP
	6.12

Structure	BIID
0,000	C ₂₆ H ₂₅ N ₅ O ₂
	CLOGP
	4.82

Structure	BIIE
D	ļ
	C ₃₀ H ₃₂ N ₄ O ₅
	CLOGP
	5.36

Structure	BIIF
90000	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂
	CLOGP
	7.51

Structure	BIIG
Ora, is	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂
	CLOGP
L	5.85

Structure	BilH
0,0000	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂
	CLOGP
	6.68

Structure	BIIK
0,000	C ₂₅ H ₂₄ N ₄ O ₂ S
	CLOGP
	5.74

Structure	BIIL
0,000	C ₂₅ H ₂₄ N ₄ O ₂ S
	CLOGP
	5.74

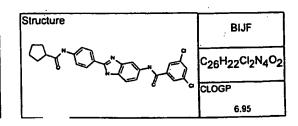
Structure	BIJA
0,000	C ₂₆ H ₂₄ N ₄ O ₂
***	CLOGP
	5.45

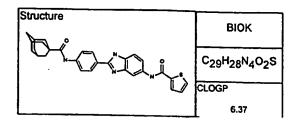
Structure	ВІЈВ
0.0 Dis.	C ₂₆ H ₂₃ CIN ₄ O ₂
	CLOGP
1	6.22

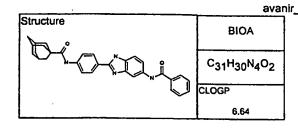
Structure	BIJC
arapio o	C ₂₇ H ₂₆ N ₄ O ₃
	CLOGP
	5.56

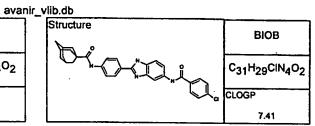
Structure	BIJD
0,000	C ₂₅ H ₂₃ N ₅ O ₂
	CLOGP
	4.26

Structure	BIJE
- !	
7000	C ₂₉ H ₃₀ N ₄ O ₅
, ,	CLOGP
	4.80









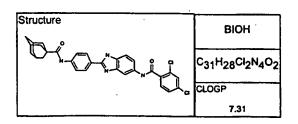
Structure	BIOC
-CALL	C ₃₂ H ₃₂ N ₄ O ₃
	CLOGP
	6.75

Structure	BIOD
	C ₃₀ H ₂₉ N ₅ O ₂
	CLOGP
	5.45

Structure	BIOE
- Cinin	C ₃₄ H ₃₆ N ₄ O ₅
	CLOGP
	5.99

Structure	BIOF
De -	
	C ₃₁ H ₂₈ Cl ₂ N ₄ O ₂
Y	CLOGP
	8.14

Structure	BIOG
D'O Dii	C ₃₁ H ₂₈ Cl ₂ N ₄ O ₂
	CLOGP
	6.48



Structure	BIPG
Orano O	C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂
	CLOGP
	6.41

Structure	ВІРН
و المربي م	C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂
	CLOGP
	7.24

Structure	вірк
0,0000	C ₂₆ H ₂₆ N ₄ O ₂ S
	CLOGP
	6.30

Structure	BIPL
0,00,00	C ₂₆ H ₂₆ N ₄ O ₂ S
N —	CLOGP
	6.30

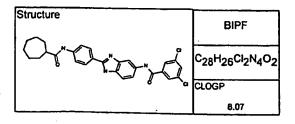
Structure	BIPA
0,000	C ₂₈ H ₂₈ N ₄ O ₂
	CLOGP
	6.57

Structure	BIPB
	DIFB
Cicio de	C ₂₈ H ₂₇ CIN ₄ O ₂
	CLOGP
	7.34

Structure	BIPC
0,0000	C ₂₉ H ₃₀ N ₄ O ₃
"-	CLOGP
	6.68

Structure	BIPD
0,000	C ₂₇ H ₂₇ N ₅ O ₂
	CLOGP
	5.38

Structure	BIPE
Orani,	C ₃₁ H ₃₄ N ₄ O ₅
	CLOGP
	5.92



Structure .	BIQA	Structure 2	BIQB
Structure	C ₂₈ H ₂₆ N ₄ O ₂	Structure	C ₂₈ H ₂₅ CIN ₄ O ₂
ξ.	CLOGP 5.76	ζ	CLOGP 6.54
	<u></u>		<u>, , , , , , , , , , , , , , , , , , , </u>
Structure	BIQC	Structure	BIQD
Structure of o	C ₂₉ H ₂₈ N ₄ O ₃	Sudding Signature	C ₂₇ H ₂₅ N ₅ O ₂
Ą	CLOGP 5.88	ර්	CLOGP 4.57
Structure	BIQE	Structure	BIQF
Structure	C ₃₁ H ₃₂ N ₄ O ₅	or or	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₂
\$,	CLOGP 5.11	-à	CLOGP 7,27
Structure	BIQG	Structure &	BIQH
Structure	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₂	or or	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₂
\ \\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	CLOGP 5.61	Š	CLOGP 6.44
Structure	BIQK	Structure	BIQL
्रेट इ.	C ₂₆ H ₂₄ N ₄ O ₂ S	Structure . A	C ₂₆ H ₂₄ N ₄ O ₂ S
<u> </u>	CLOGP 5.50	3	CLOGP 5.50

	_
Structure	BIRL
28 77	C ₂₆ H ₂₂ N ₄ O ₂ S
→ ↓	CLOGP
	5.02
Structure	BIRH
	C ₂₈ H ₂₂ Cl ₂ N ₄ O ₂
² \$	CLOGP
β.	5.95
·	
Structure	BIRB
	C28H23CIN4O2
귀ㅣ 옻	CLOGP
	6.05
Structure	BIRD
03 20	C ₂₇ H ₂₃ N ₅ O ₂
- 	CLOGP
	4.09
Structure	BIRF
	Dil.vi
405	C ₂₈ H ₂₂ Cl ₂ N ₄ O ₂
7 3	CLOGP 6.78
1 1	
	Structure Structure Structure Structure Structure

In accordance with another aspect of the present invention, there is disclosed a method for the preparation of a medicament for treatment of a condition associated with an excess IgE level. The compound has the formula:

X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF₃, OCF₃, CONH₂, CONHR and NHCOR₁. R is selected from the group consisting of H, CH₃, C₂H₅, C₃H₇, C₄H₉, CH₂Ph, and CH₂C₆H₄-F(p-). R₁ and R₂ are independently selected from the group consisting of H, aryl, substituted aryl, cycloaryl substituted cycloaryl, multi-ring cycloaryl, benzyl, substituted benzyl and the like. Substitutions are alkyl, aryl, CF₃, CH₃, OCH₃, OH, CN, COOR, COOH and the like.

In accordance with another aspect of the present invention, there is disclosed a method of treating a mammal having a condition associated with an excess IgE level. The method comprises administering to the mammal an amount of a compound sufficient to reduced IgE levels in the mammal. The compound has the formula:

X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF₃, OCF₃, CONH₂, CONHR and NHCOR₁. R is selected from the group consisting of H, CH₃, C₂H₅, C₃H₇, C₄H₉,

CH₂Ph, and CH₂C₆H₄-F(p-). R₁ and R₂ are independently selected from the group consisting of H, aryl, substituted aryl, cycloaryl substituted cycloaryl, multi-ring cycloaryl, benzyl, substituted benzyl, alkyl, cycloalkyl substituted cycloalkyl, multi-ring cycloalkyl, fused-ring aliphatic, cyclopropyl, substituted cyclopropyl, substituted cyclobutyl, cyclopentyl, substituted cyclopentyl, cyclopentyl, substituted cyclohexyl, substituted cycloheptyl, bicycloheptyl, bicyclooctyl, bicyclononyl, substituted bicycloalknyl, adamantyl, substituted adamantyl and the like, wherein at least one of R1 and R2 are aromatic groups. Substitutions are alkyl, aryl, CF3, CH3, OCH₃, OH, CN, COOR, COOH and the like.

In a variation of the above-disclosed method, at least one additional active ingredient may be administered in conjunction with the administration of the compound. The additional active ingredient may be combined with said compound in a pharmaceutically acceptable diluent and co-administered to the mammal. The additional active ingredient may be a short-acting β_2 -adrenergic agonist selected from the group consisting of terbutaline and albuterol. In a variation, the additional active ingredient may be a long-acting β_2 -adrenergic agonist selected from the group consisting of salmeterol and formoterol or an antihistamine selected from the group consisting of loratadine, azelastine and ketotifen. In another variation, the additional active ingredient may be a phosphodiesterase inhibitor, an anticholinergic agent, a corticosteroid, an inflammatory mediator release inhibitor or a leukotriene receptor antagonist.

The compound is preferably administered at a dose of about 0.01 mg to about 100 mg per kg body weight per day in divided doses of said compound for at least two consecutive days at regular periodic intervals.

Other variations within the scope of the present invention may be more fully understood with reference to the following detailed description.

Detailed Description of the Preferred Embodiment

The present invention is directed to small molecule inhibitors of IgE (synthesis and/or release) which are useful in the treatment of allergy and/or asthma or any diseases where IgE is pathogenic. The particular compounds disclosed herein were identified by their ability to suppress IgE levels in both ex vivo and in vivo assays. Development and optimization of clinical treatment regimens can be monitored by those of skill in the art by reference to the ex vivo and in vivo assays described below.

Ex Vivo Assay

This assay begins with *in vivo* antigen priming and measures secondary antibody responses *in vitro*. The basic protocol was documented and optimized for a range of parameters including: antigen dose for priming and time span following priming, number of cells cultured *in vitro*, antigen concentrations for eliciting secondary IgE (and other Ig's) response *in vitro*, fetal bovine serum (FBS) batch that will permit optimal IgE response *in vitro*, the importance of primed CD4+ T cells and hapten-specific B cells, and specificity of the ELISA assay for IgE (Marcelletti and Katz, *Cellular Immunology* 135:471-489 (1991); incorporated herein by reference).

The actual protocol utilized for this project was adapted for a more high throughput analyses. BALB/cByj mice were immunized i.p. with 10 μ g DNP-KLH adsorbed onto 4 mg alum and sacrificed after 15 days. Spleens were excised and homogenized in a tissue grinder, washed twice, and maintained in DMEM supplemented with 10% FBS, 100 U/ml penicillin, 100 μ g/ml streptomycin and 0.0005% 2-mercaptoethanol. Spleen cell cultures were established (2-3 million cells/ml, 0.2 ml/well in quadruplicate, 96-well plates) in the presence or absence of DNP-KLH (10 ng/ml). Test compounds (2 μ g/ml and 50 ng/ml) were added to the spleen cell cultures containing antigen and incubated at 37° C for 8 days in an atmosphere of 10% CO₂.

Culture supernatants were collected after 8 days and Ig's were measured by a modification of the specific isotype-selective ELISA assay described by Marcelletti and Katz (Supra). The assay was modified to facilitate high throughput. ELISA plates were prepared by coating with DNP-KLH overnight. After blocking with bovine serum albumin (BSA), an aliquot of each culture supernatant was diluted (1:4 in phosphate buffered saline (PBS) with BSA, sodium azide and Tween 20), added to the ELISA plates, and incubated overnight in a humidified box at 4° C. IgE levels were quantitated following successive incubations with biotinylated-goat antimouse IgE (b-GAME), AP-streptavidin and substrate.

Antigen-specific IgG1 was measured similarly, except that culture supernatants were diluted 200-fold and biotinylated-goat antimouse IgG1 (b-GAMG1) was substituted for b-GAME. IgG2a was measured in ELISA plates that were coated with DNP-KLH following a 1:20 dilution of culture supernatants and incubation with biotinylated-goat antimouse IgG2a (b-GAMG2a). Quantitation of each isotype was determined by comparison to a standard curve. The level of detectability of all

antibody was about 200-400 pg/ml and there was less than 0.001% cross-reactivity with any other Ig isotype in the ELISA for IgE.

In Vivo Assay

Compounds found to be active in the ex vivo assay (above) were further tested for their activity in suppressing IgE responses in vivo. Mice receiving low-dose radiation prior to immunization with a carrier exhibited an enhanced IgE response to sensitization with antigen 7 days later. Administration of the test compounds immediately prior to and after antigen sensitization, measured the ability of that drug to suppress the IgE response. The levels of IgE, IgG1 and IgG2a in serum were compared.

Female BALB/cByj mice were irradiated with 250 rads 7 hours after initiation of the daily light cycle. Two hours later, the mice were immunized i.p. with 2 μ g of KLH in 4 mg alum. Two to seven consecutive days of drug injections were initiated 6 days later on either a once or twice daily basis. Typically, i.p. injections and oral gavages were administered as suspensions (150 μ l/injection) in saline with 10% ethanol and 0.25% methylcellulose. Each treatment group was composed of 5-6 mice. On the second day of drug administration, 2 μ g of DNP-KLH was administered i.p. in 4 mg alum, immediately following the morning injection of drug. Mice were bled 7-21 days following DNP-KLH challenge.

Antigen-specific IgE, IgG1 and IgG2a antibodies were measured by ELISA. Periorbital bleeds were centrifuged at 14,000 rpm for 10 min, the supernatants were diluted 5-fold in saline, and centrifuged again. Antibody concentrations of each bleed were determined by ELISA of four dilutions (in triplicate) and compared to a standard curve: anti-DNP IgE (1:100 to 1:800), anti-DNP IgG2a (1:100 to 1:800), and anti-DNP IgG1 (1:1600 to 1:12800).

Diacyl Benzimidazole Inhibitors of IgE

Several species embraced by the following generic formula were synthesized and evaluated for their effectiveness in down-regulating IgE in the ex vivo and in vivo assays.

X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF₃, OCF₃, CONH₂, CONHR and NHCOR₁. R is selected from the group consisting of H, CH₃, C₂H₅, C₃H₇, C₄H₉, CH₂Ph, and CH₂C₆H₄-F(p-). R₁ and R₂ are independently selected from the group consisting of H, aryl, substituted aryl, cycloaryl substituted cycloaryl, multi-ring cycloaryl, benzyl, substituted benzyl, alkyl, cycloalkyl substituted cycloalkyl, multi-ring cycloalkyl, fused-ring aliphatic, cyclopropyl, substituted cyclopropyl, substituted cyclobutyl, substituted cyclopentyl, substituted cyclopentyl, bicyclopentyl, substituted cyclohexyl, substituted cycloheptyl, bicycloheptyl, bicyclooctyl, bicyclononyl, substituted bicycloalknyl, adamantyl, substituted adamantyl and the like, wherein at least one of R1 and R2 are aromatic groups. Substitutions are alkyl, aryl, CF3, CH3, OCH₃, OH, CN, COOR, COOH and the like.

Synthesis of the Combinatorial Library

The diacyl benzimidazole compounds of the present invention were prepared using the following synthesis reactions, wherein the desired acid chlorides are selected from the R1 and R2 groups provided in the Table.

Synthesis of 3: 4-Nitro-1,2-phenylenediamine (10 g, 65.3 mmol) and 4-aminobenzoic acid (8.95 g, 65.3 mmol) were taken in a round bottomed flask and phosphorus oxychloride (95 ml) was added slowly. The reaction mixture was allowed to stir under reflux conditions. After 18 h, the reaction was allowed to cool and then poured slowly into an ice water mixture in an Erlenmeyer flask with vigorous stirring. Greenish yellow precipitate fell out which was then

filtered and washed with copious amounts of water. The residue was then dried to obtain 16.9 g of crude desired product. Mass spectrum analysis (positive ion) indicated presence of 3.

Synthesis of 4: Benzimidazole 3 (800 mg, 3.14 mmol) was dissolved in dry pyridine (5 ml) in a scintillation vial and the desired acid chlorides (1.1 eq) were added slowly. The reactions were carried out in an oven at 60C. After 16h, the reaction was cooled to RT and DI water was added. Precipitation took place, which was filtered off, washed with water and air dried. The aqueous layer was extracted with EtOAc (6 x 50 ml), dried over anhydrous Na₂SO₄ and the solvent was removed *in vacuo* to result in a colored solid. By positive ion MS the desired monoacylated product was found to be present in the initial precipitate as well as in the organic layer. Hence the solid residues obtained were combined and used as such for the reduction step.

Reduction of 4: Crude monoacylated nitro benzimidazole 4 (1.22 g, 3.40 mmol) was dissolved in MeOH (20 ml) and minimum amount of THF was added for complete dissolution to occur. Catalytic amount of 10% Pd on C was added and the solution was degassed and allowed to stir at 3.4 atm pressure under H₂ atmosphere for 4 h. Upon completion of reaction as observed via TLC, the reaction mixture was filtered through celite and the solvent was removed under reduced pressure to afford 979 mg of crude residue.

General Organic Analyses

HPLC/MS data was obtained using a Gilson semi-prep HPLC with a Gilson 170 Diode Array UV detector and PE Sciex API 100LC MS based detector. A Waters 600E with a Waters 490E UV detector was also used for recording HPLC data. The compounds were eluted with a gradient of CH₃CN (with 0.0035% TFA) and H₂O(with 0.01% TFA). Both HPLC instruments used Advantage C18 60A 5μ 50mm x 4.6mm columns from Thomson Instrument Company. Mass spectra were obtained by direct injection and electrospray ionization on a PE Sciex API 100LC MS based detector. Thin layer chromatography was performed using Merck 60F-254 aluminum backed precoated plates. Flash chromatography was carried out on Merck silica gel 60 (230-400 mesh) purchased from EM Scientific.

Syntheses of Symmetrical Diamides

The symmetrical diacyl benzimidazole compounds of the present invention were generally prepared from 2-(4-aminophenyl)-5-aminobenzimidazole, which was obtained by reduction of 2-(4-nitrophenyl)-6-nitrobenzimidazole.

2-(4-nitrophenyl)-6-nitrobenzimidazole

The dinitro benzimidazole was prepared as follows: a mixture of 4-nitrophenylenediamine (6.4g, 41.83 mmol) and 4-nitrobenzoic acid (7.86 g, 47 mmol) was dissolved in POCl₃ (250 ml) and heated to reflux for 2 h. The reaction mixture was cooled, poured on to ice, and stirred for 30 min. The resulting solid was filtered and washed with methanol and sodium bicarbonate to remove unreacted acid and allowed to dry overnight to give the desired product as a brown solid (5.8 g). The product was characterized by electrospray mass spectroscopy (mp >300° C).

2-(4-Aminophenyl)-5-aminobenzimidazole was prepared by suspending the above solid (75 g) in THF (75 ml), to which was added Pd-C (10% Pd by weight). The flask was purged with hydrogen and stirred under a balloon of hydrogen over night. TLC and MS showed starting material was still present so the reaction was allowed to continue over the weekend. TLC indicated complete reaction, the reaction was filtered through celite and washed with methanol. The solvent was removed under reduced pressure to give a dark brown solid (0.37 g) that was used without further purification.

Alternatively, the 2-(4-aminophenyl)-5-aminobenzimidazole was prepared by the following reduction: 2-(4-nitrophenyl)-6-nitrobenzimidazole (8.9 g, 31 mmole) was suspended in concentrated HCl (100 ml) to which was added stannous chloride (42.3 g 180 mmole). The reaction mixture was heated to reflux for 5 hrs. The mixture was cooled to RT and the HCl salt

of the desired product was precipitated by the addition of ethanol. The resulting solid was filtered, re-dissolved in water and the solution made basic by the addition of concentrated ammonium hydroxide. The resulting precipitate was filtered and dried overnight under vacuum to yield the desired product as a gray solid (6.023 g, 26.9 mmole, 87%). The product characterized by electrospray mass spectroscopy and HPLC (mp. 222-227° C).

2-(4-Aminophenyl)-5-methoxy benzimidazole was synthesized from 2-(4-nitrophenyl)-5-methoxy benzimidazole, which was prepared as follows: 1,2-diamino-4-methoxybenzene (1.26 g, 10.0 mmole was mixed with 4-nitrobenzoic acid (1.67 g, 9.8 mmole) and dissolved in POCl₃ (10 ml) and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured onto ice. The resulting solid was filtered, washed with NaHCO₃ and used without further purification.

2-(4-nitrophenyl)-5-methoxy benzimidazole

2-(4-Aminophenyl)-5-methoxy benzimidazole was prepared by dissolving 1 g of the above nitrobenzimidazole in 30% Na₂S•9H₂O (20 ml) with stirring at RT for 21 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.

2-(4-aminophenyl)-5-methoxy benzimidazole

2-(4-Aminophenyl)-5,6-dichloro benzimidazole was synthesized from 2-(4-nitrophenyl)-5,6-dichloro benzimidazole, which was prepared as follows: 1,2-diamino-4,5-dichlorobenzene (1.68 g, 10.0 mmole) was mixed with 4-nitrobenzoic acid (1.58 g, 9.3 mmole), dissolved in POCl₃ (10 ml), and heated to reflux for 2.5 hours. The reaction mixture was cooled and

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cautiously poured onto ice. The resulting solid was filtered, washed with NaHCO₃ and used without further purification.

2-(4-nitrophenyl)-5,6-dichloro benzimidazole

2-(4-Aminophenyl)-5,6-dichloro benzimidazole was prepared by dissolving 1 g of the above nitrobenzimidazole in 30% Na₂S•9H₂O (20 ml) with stirring at RT for 21 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.

2-(4-Aminophenyl)-5,6-dichloro benzimidazole

2-(4-aminophenyl)-7-methyl benzimidazole was synthesized from 2-(4-nitrophenyl)-7-methyl benzimidazole, which was prepared by mixing 1,2-diamino-3-methylbenzene (1.24 g, 10.0 mmole) with 4-nitrobenzoic acid (1.69 g, 9.8 mmole), dissolved in POCl₃ (10 ml), and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured onto ice. The resulting solid was filtered, washed with NaHCO₃ and used without further purification.

2-(4-nitrophenyl)-7-methyl benzimidazole

2-(4-Aminophenyl)-7-methyl benzimidazole was synthesized by dissolving 1 g of the above nitrobenzimidazole in 30% Na₂S•9H₂O (20 ml) with stirring at RT for 4.5 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were

dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.

2-(4-aminophenyl)-7-methyl benzimidazole

2-(4-Aminophenyl)-6-methyl benzimidazole was synthesized from 2-(4-nitrophenyl)-6-methyl benzimidazole, which was prepared by mixing 1,2-diamino-4-methylbenzene (1.24 g, 9.8 mmole) with 4-nitrobenzoic acid (1.6 g, 9.9 mmole) and dissolved in POCl₃ (10 ml) and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured onto ice. The resulting solid was filtered, washed with NaHCO₃ and used without further purification.

2-(4-nitrophenyl)-6-methyl benzimidazole

2-(4-Aminophenyl)-6-methyl benzimidazole was synthesized by dissolving 1 g of the above nitrobenzimidazole in 30% Na₂S•9H₂O (20 ml) with stirring at RT for 4.5 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.

2-(4-aminophenyl)-6-methyl benzimidazole

2-(4-Aminophenyl)-5,6-dimethyl benzimidazole was synthesized from 2-(4-nitrophenyl)-5,6-dimethyl benzimidazole, which was prepared by mixing 1,2-diamino-4,5-dimethylbenzene (1.38 g, 10.1 mmole) with 4-nitrobenzoic acid (1.69 g, 9.9 mmole) and dissolved in POCl₃ (10 ml) and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured

onto ice. The resulting solid was filtered, washed with NaHCO₃ and used without further purification.

2-(4-nitrophenyl)-5,6-dimethyl benzimidazole

2-(4-Aminophenyl)-5,6-dimethyl benzimidazole was synthesized by dissolving 1 g of the above nitrobenzimidazole (31.1) in 30% Na₂S•9H₂O (20 ml) with stirring at RT for 4.5 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.

2-(4-aminophenyl)-5,6-dimethyl benzimidazole

The subsequent preparation of symmetrical diamides was accomplished by one of the following methods:

Method A: 2-(4-Aminophenyl)-6-aminobenzimidazole (1 mmole) was suspended in THF (5 ml) to which was added DIEA (2.5 mmole) and mixture cooled to -78° C. To the above cooled mixture was added the acid chloride (2.5 mmole) and let warm to RT overnight. Water (2 ml) is added to the reaction and extracted with EtOAc. The combined organic extracts were combined washed with NaHCO₃ (aq.) and concentrated under reduced pressure. The resulting residue was purified on silica gel (hexanes/EtOAc or MeOH/CH₂Cl₂) or reverse phase HPLC (CH₃CN/H₂O).

Method B: 2-(4-Aminophenyl)-6-aminobenzimidazole (1 mmole) and DMAP (cat.) was dissolved in pyridine (5 ml). To the above solution was added the acid chloride (2.5 mmole) and the reaction stirred overnight at 60° C. The reaction was cooled to room temperature and water added to precipitate the product. The resulting solid was collected by filtration with the solid

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being washed by hexanes and water and NaHCO₃ (aq.). The resulting residue was purified on silica gel (hexanes/EtOAc or MeOH/CH₂Cl₂) or reverse phase HPLC (CH₃CN/H₂O).

Method C: 2-(4-Aminophenyl)-6-aminobenzimidazole (1 mmole) was suspended in THF (10 ml) to which was added K₂CO₃ (2.5 mmole) in water (0.5 ml). and mixture cooled to -78° C. To the above cooled mixture was added the acid chloride (2.5 mmole) and let warm to RT overnight. Water (10 ml) was added to the reaction and extracted with EtOAc. The combined organic extracts were combined washed with NaHCO₃ (aq.) and concentrated under reduced pressure. The resulting residue was purified on silica gel (hexanes/EtOAc or MeOH/CH₂Cl₂) or reverse phase HPLC (CH₃CN/H₂O).

Method D: The carboxylic acid (2.2 mmole), EDC (2.2 mmole) and DMAP (cat.) was dissolved in hot pyridine. To the above solution was added 2-(4-aminophenyl)-6-aminobenzimidazole (1 mmole) and heated to 60° C overnight. The cooled reaction mixture was partitioned between water and EtOAc. The organic layer was washed with NaHCO₃, dried over Na₂SO₄ and concentrated under vacuum. The resulting residue was purified on silica gel (hexanes/EtOAc or MeOH/CH₂Cl₂) or reverse phase HPLC (CH₃CN/H₂O).

Diacyl Benzimidazole Species

The following species encompassed within the disclosed generic formula were synthesized and tested for their ability to suppress IgE. The species are presented above in the Summary of the Invention

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IgE Down-Regulatory Activity

All of the disclosed species were tested for their ability to suppress IgE in both the ex vivo and in vivo assays. They were all active in both assays. Activities (IC50) of the species in the ex vivo assay ranged from about 100 pM to 1 nM. In the in vivo assay, the IC50 dose ranged from approximately 100 µg/kg body weight/day to about 10 mg/kg body weight/day. The diacyl benzimidazole compounds were generally more potent than the monoacyl compounds.

Suppression of IgE Response

The inhibitory activity of the small molecules of the present invention were assayed using both the ex vivo and in vivo assays as described above. All of the compounds presented above were active in suppressing the IgE response. In the ex vivo assay, compounds in genuses I-XI produced 50% inhibition at concentrations ranging from 1 pM to 10 μM. In the in vivo assay, the compounds were effective at concentrations ranging from less than about 0.01 mg/kg/day to about 25 mg/kg/day, when administered in divided doses (e.g., two to four times daily) for at least two to seven consecutive days. Thus, the small molecule inhibitors of the present invention are disclosed as being useful in lowering the antigen-induced increase in IgE concentration, and consequently, in the treatment of IgE-dependent processes such as allergies in general and allergic asthma in particular.

Treatment Regimens

The amount of the IgE inhibitor compound which may be effective in treating a particular allergy or condition will depend on the nature of the disorder, and can be determined by standard clinical techniques. The precise dose to be employed in a given situation will also depend on the choice of compound and the seriousness of the condition, and should be decided according to the judgment of the practitioner and each patient's circumstances. Appropriate dosages can be determined and adjusted by the practitioner based on dose response relationships between the patient's IgE levels as well as standard indices of pulmonary and hemodynamic changes. Moreover, those skilled in the art will appreciate that dose ranges can be determined without undue experimentation by following the protocol(s) disclosed herein for ex vivo and in vivo screening (See for example Hasegawa et al., *J. Med. Chem.* 40: 395-407 (1997) and Ohmori et al., *Int. J. Immunopharmacol.* 15:573-579 (1993); employing similar ex vivo and in vivo assays for determining dose-response relationships for IgE suppression by naphthalene derivatives; incorporated herein by reference).

Initially, suitable dosages of the compounds will generally range from about 0.001 mg to about 300 mg per kg body weight per day in divided doses, more preferably, between about 0.01 mg and 100 mg per kg body weight per day in divided doses. The compounds are preferably administered systemically as pharmaceutical formulations appropriate to such routes as oral. aerosol, intravenous, subcutaneously, or by any other route which may be effective in providing systemic dosing of the active compound. The compositions of pharmaceutical formulations are well known in the art. The treatment regimen preferably involves periodic administration. Moreover, long-term therapy may be indicated where allergic reactions appear to be triggered by continuous exposure to the allergen(s). Daily or twice daily administration has been effective in suppressing the IgE response to a single antigen challenge in animals when carried out continuously from a period of two to seven consecutive days. Thus, in a preferred embodiment, the compound is administered for at least two consecutive days at regular periodic intervals. However, the treatment regimen, including frequency of dosing and duration of treatment may be determined by the skilled practitioner, and modified as needed to provide optimal IgE down-regulation, depending on nature of the allergen, the dose, frequency, and duration of the allergen exposure, and the standard clinical indices.

In one embodiment of the present invention, an IgE-suppressing compound may be administered in conjunction with one or more of the other small molecule inhibitors disclosed, in order to produce optimal down-regulation of the patient's IgE response. Further, it is envisioned that one or more of the compounds of the present invention may be administered in combination with other drugs already known or later discovered for treatment of the underlying cause as well as the acute symptoms of allergy or asthma. Such combination therapies envisioned within the scope of the present invention include mixing of one or more of the small molecule IgE-inhibitors together with one or more additional ingredients, known to be effective in reducing at least one symptom of the disease condition. In a variation, the small molecule IgE-inhibitors herein disclosed may be administered separately from the additional drugs, but during the same course of the disease

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condition, wherein both the IgE-inhibitor(s) and the palliative compounds are administered in accordance with their independent effective treatment regimens.

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WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising the following compounds:

wherein X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF₃, OCF₃, CONH₂, CONHR and NHCOR₁;

wherein R is selected from the group consisting of H, CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , CH_2Ph , and $CH_2C_6H_4$ -F(p-); and

wherein R₁ and R₂ are independently selected from the group consisting of H, aryl, substituted aryl, cycloaryl substituted cycloaryl, multi-ring cycloaryl, benzyl, substituted benzyl, alkyl, cycloalkyl substituted cycloalkyl, multi-ring cycloalkyl, fused-ring aliphatic, cyclopropyl, substituted cyclopropyl, substituted cyclobutyl, substituted cyclopentyl, substituted cyclohexyl, substituted cyclohexyl, substituted cyclohexyl, bicyclonoryl, bicyclonoryl, substituted bicycloalknyl, adamantyl, substituted adamantyl and the like, wherein at least one of R1 and R2 are aromatic groups.

- 2. The pharmaceutical composition of claim 1, wherein the R₁ and R₂ substitutions are selected from the group consisting of alkyl, aryl, CF₃, CH₃, OCH₃, OH, CN, COOR and COOH.
- 3. The pharmaceutical composition of Claim 2, wherein the compound is selected from the group consisting of:

Structure	BIAA
0,000	C ₂₇ H ₂₀ N ₄ O ₂
	CLOGP
	5.47

· <u></u>	
Structure	BIAB
dediso.	C ₂₇ H ₁₉ CIN ₄ O ₂
	CLOGP
1	6.24

Structure	BIAC
aranio"	C ₂₈ H ₂₂ N ₄ O ₃
	CLOGP
	5.58

Structure .	BIAD
0,0000	C ₂₆ H ₁₉ N ₅ O ₂
	CLOGP
	4.28

Structure	BIAE
orang.	C ₃₀ H ₂₆ N ₄ O ₅
	CLOGP
	4.82

Structure	BIAF
0,0,0,0	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂
	CLOGP
	6.97

Structure	BIAG
Giropo	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂
h—/ a	CLOGP
	5.31

Structure	ВІАН
	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂
	CLOGP
	6.14

Structure	BIAI
0,000	C ₂₇ H ₂₆ N ₄ O ₂
	CLOGP
	6.01

Structure	BIAJ
0,000	C ₂₆ H ₂₄ N ₄ O ₂
"-"	CLOGP
	5.45

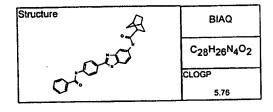
Structure	BIAK
Orano o	C ₂₅ H ₁₈ N ₄ O ₂ S
	CLOGP
	5.20

Structure	BIAM
	° C ₃₀ H ₂₄ N ₄ O ₂
	CLOGP 5.74
Structure	BIAO

Structure	BIAN
0,017	C ₂₂ H ₁₈ N ₄ O ₂
	CLOGP
	3.98

Structure	BIAO
	C ₃₁ H ₃₀ N ₄ O ₂
	CLOGP
	6.64

Structure	BIAP
0,000	C ₂₈ H ₂₈ N ₄ O ₂
•	CLOGP
	6.57



Structure	A	BIAR
	بر ال	C ₂₈ H ₂₄ N ₄ O ₂
امتا	J	CLOGP
0.		5.28

Structure	BIBA
Orano O	C ₂₇ H ₁₉ CIN ₄ O ₂
H	CLOGP
	6.26

Structure	BIBB
orano.	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂
"	CLOGP
	7.04

Structure	BIBC
'oragio'	C ₂₈ H ₂₁ CIN ₄ O ₃
	CLOGP
	6.38

Structure	BIBD
0,000	C ₂₆ H ₁₈ CIN ₅ O ₂
	CLOGP
	5.08

Structure	BIBE
orani.	C ₃₀ H ₂₅ CIN ₄ O ₅
° '	CLOGP
	5.62

		• • • • • • • • • • • • • • • • • • • •	
Structure	BIBG	Structure	ВІВН
dinoro	C ₂₇ H ₁₇ Cl ₃ N ₄ O ₂	orano.	C ₂₇ H ₁₇ Cl ₃ N ₄ O ₂
h-1 a	CLOGP	•••	CLOGP
	6.11		6.94
·			
Structure	BIBI	Structure	BIBJ
Of Or Day	C ₂₇ H ₂₅ CIN ₄ O ₂	Of Or Or O	C ₂₆ H ₂₃ CIN ₄ O ₂
H-4-	CLOGP		CLOGP
	6.81		6.25
Structure	BIBK	Structure	BIBL
Of Orongo	C ₂₅ H ₁₇ CIN ₄ O ₂ S	"Orono"	C ₂₅ H ₁₇ CIN ₄ O ₂ S
I	CLOGP	-	CLOGP
	6.00		6.00
Structure	ВІВМ	Structure	BIBN
Structure	BIBM C ₃₀ H ₂₃ CIN ₄ O ₂	Structure	BIBN C ₂₂ H ₁₇ CIN ₄ O ₂
Structure		Structure	ļ
Structure	C ₃₀ H ₂₃ CIN ₄ O ₂	Structure	C ₂₂ H ₁₇ CIN ₄ O ₂
Structure	C ₃₀ H ₂₃ CIN ₄ O ₂	Structure	C ₂₂ H ₁₇ CIN ₄ O ₂
Structure	C ₃₀ H ₂₃ CIN ₄ O ₂	Structure	C ₂₂ H ₁₇ CIN ₄ O ₂
محري م	C ₃₀ H ₂₃ CIN ₄ O ₂ CLOGP 6.54		C ₂₂ H ₁₇ CIN ₄ O ₂ CLOGP 4.78
محري م	C ₃₀ H ₂₃ CIN ₄ O ₂ CLOGP 6.54		CLOGP 4.78
محري م	C ₃₀ H ₂₃ CIN ₄ O ₂ CLOGP 6.54 BIBO C ₃₁ H ₂₉ CIN ₄ O ₂		C ₂₂ H ₁₇ CIN ₄ O ₂ CLOGP 4.78 BIBP C ₂₈ H ₂₇ CIN ₄ O ₂
Structure	C ₃₀ H ₂₃ CIN ₄ O ₂ CLOGP 6.54 BIBO C ₃₁ H ₂₉ CIN ₄ O ₂ CLOGP	Structure Character Character	C ₂₂ H ₁₇ CIN ₄ O ₂ CLOGP 4.78 BIBP C ₂₈ H ₂₇ CIN ₄ O ₂ CLOGP
Structure	C ₃₀ H ₂₃ CIN ₄ O ₂ CLOGP 6.54 BIBO C ₃₁ H ₂₉ CIN ₄ O ₂ CLOGP	Structure Structure	C ₂₂ H ₁₇ CIN ₄ O ₂ CLOGP 4.78 BIBP C ₂₈ H ₂₇ CIN ₄ O ₂ CLOGP
Structure	C ₃₀ H ₂₃ CIN ₄ O ₂ CLOGP 6.54 BIBO C ₃₁ H ₂₉ CIN ₄ O ₂ CLOGP 7.43	Structure Structure	C ₂₂ H ₁₇ CIN ₄ O ₂ CLOGP 4.78 BIBP C ₂₈ H ₂₇ CIN ₄ O ₂ CLOGP 7.37
Structure	C ₃₀ H ₂₃ CIN ₄ O ₂ CLOGP 6.54 BIBO C ₃₁ H ₂₉ CIN ₄ O ₂ CLOGP 7.43 BIBQ C ₂₈ H ₂₅ CIN ₄ O ₂	Structure Structure	C ₂₂ H ₁₇ CIN ₄ O ₂ CLOGP 4.78 BIBP C ₂₈ H ₂₇ CIN ₄ O ₂ CLOGP 7.37 BIBR C ₂₈ H ₂₃ CIN ₄ O ₂
Structure	C ₃₀ H ₂₃ CIN ₄ O ₂ CLOGP 6.54 BIBO C ₃₁ H ₂₉ CIN ₄ O ₂ CLOGP 7.43	Structure Character Character	C ₂₂ H ₁₇ CIN ₄ O ₂ CLOGP 4.78 BIBP C ₂₈ H ₂₇ CIN ₄ O ₂ CLOGP 7.37

Structure	BICA
Organio O	C ₂₈ H ₂₂ N ₄ O ₃
	CLOGP
	5.58

Structure	BICB
, olding.	C ₂₈ H ₂₁ CIN ₄ O ₃
	CLOGP
	6.35

Structure	BICC
oranio"	C ₂₉ H ₂₄ N ₄ O ₄
	CLOGP
	5.70

Structure	BICD
Orano Po	C ₂₇ H ₂₁ N ₅ O ₃
	CLOGP
	4.39

Structure	BICE
"Orogona"	C ₃₁ H ₂₈ N ₄ O ₆
,	CLOGP
	4,93

Structure	BICF
orogono.	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃
100	CLOGP
	. 7.09

Structure	BICG
(inoro	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃
• • • • • • • • • • • • • • • • • • • •	CLOGP
	5.43

Structure	вісн
· Organio	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃
	CLOGP
	6.26

Structure	BICI
of agrico	C ₂₈ H ₂₈ N ₄ O ₃
	CLOGP
	6.12

Structure	BICJ
of ago of	C ₂₇ H ₂₆ N ₄ O ₃
	CLOGP
	5.56

Structure	BICK
Of Original O	C ₂₆ H ₂₀ N ₄ O ₃ S
	CLOGP
	5.32

6.10

Structure	вісм	Structure	BICN
00000	C ₃₁ H ₂₆ N ₄ O ₃	"Or Och	C ₂₃ H ₂₀ N ₄ O ₃
	CLOGP		CLOGP
	5.85		4.09
Structure	BICO	Structure	BICP
	C ₃₂ H ₃₂ N ₄ O ₃	O. China	C ₂₉ H ₃₀ N ₄ O ₃
	CLOGP 6.75		CLOGP 6.68
Structure	BICQ	Structure	BICR
rotoio	C ₂₉ H ₂₈ N ₄ O ₃	, oioid	C ₂₉ H ₂₆ N ₄ O ₃
, oi.	CLOGP	, O .	CLOGP 5.39
	5.88		3.39
Structure	BIDA	Structure	BIDB
0,000	C ₂₆ H ₁₉ N ₅ O ₂	٥٠٥٠٠٥	C ₂₆ H ₁₈ CIN ₅ O ₂
	CLOGP		CLOGP
	4.60		5.37
			}
Structure	BIDC	Structure	BIDD
Oranio"	C ₂₇ H ₂₁ N ₅ O ₃	China Co	C ₂₅ H ₁₈ N ₆ O ₂
	CLOGP		CLOGP
	4.71		3.41
Structure	BIDE	Structure	BIDF
Gram L.	C ₂₉ H ₂₅ N ₅ O ₅	aran 3	C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂
Jano M.	CLOGP		CLOGP

3.95

Structure BIDI C26H17Cl2N5O2 CLOGP 4.44 Structure BIDI C26H25N5O2 CLOGP 5.14 Structure BIDL C26H25N5O2 CLOGP 6.14 Structure BIDL C26H25N5O2 CLOGP 6.14 Structure BIDL C26H25N5O2 CLOGP 4.88 Structure BIDL C24H17N5O2S CLOGP 4.33 Structure BIDN C29H23N5O2 CLOGP 4.33 Structure BIDN C29H23N5O2 CLOGP 6.00GP 3.11 Structure BIDN C29H23N5O2 CLOGP 6.77 Structure BIDN C29H23N5O2 CLOGP 6.77 Structure BIDN C29H23N5O2 CLOGP 6.77 Structure BIDN C21H17N5O2 C21H17N5O2 C10GP 6.70 Structure BIDN C21H17N5O2 C10GP 6.70 Structure BIDN C21H17N5O2 C10GP 6.70 Structure BIDN BIDN C21H17N5O2 C10GP 6.70 Structure BIDN BIDN BIDN C21H17N5O2 C10GP 6.70 Structure BIDN	•			
Structure BIDI C28H25N5O2 CLOGP 5.14 Structure BIDK C24H17N5O2S CLOGP 4.33 Structure BIDM C29H23N5O2 CLOGP 4.33 Structure BIDM C29H23N5O2 CLOGP 4.33 Structure BIDM C29H23N5O2 CLOGP 4.87 Structure BIDN C29H23N5O2 CLOGP 4.87 Structure BIDN C29H23N5O2 CLOGP 4.87 Structure BIDN C29H23N5O2 CLOGP 3.11 Structure BIDN C27H27N5O2 C27H27N5O2 CLOGP 5.77	Structure	BIDG	Structure	вірн
Structure BIDI C26H25N5O2 CLOGP 5.14 Structure BIDK C24H17N5O2S CLOGP 4.33 Structure BIDM C29H23N5O2 CLOGP 4.87 Structure BIDM C29H23N5O2 CLOGP 4.87 Structure BIDN C29H23N5O2 CLOGP 5.77 Structure BIDD C27H27N5O2 CLOGP 5.77	aranit	C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂	Orono	C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂
Structure BIDI C26H25N5O2 CLOGP 5.14 Structure BIDK C24H17N5O2S CLOGP 4.33 Structure BIDM C29H23N5O2 CLOGP 4.33 Structure BIDN C29H23N5O2 CLOGP 4.33 Structure BIDN C29H23N5O2 CLOGP 3.11 Structure BIDN C29H23N5O2 CLOGP 4.87 Structure BIDN C29H23N5O2 CLOGP 3.11 Structure BIDO C30H29N5O2 CLOGP 5.77		CLOGP	"	CLOGP
Structure		4.44		5.27
Structure				·
Structure BIDK C24H17N5O2S CLOGP 4.33 Structure BIDN C29H23N5O2 CLOGP 4.87 Structure BIDN C29H27N5O2 CLOGP 3.11 Structure BIDN C29H27N5O2 CLOGP 4.87 Structure BIDN C29H27N5O2 CLOGP 5.77	Structure	BIDI	Structure	BIDJ
Structure BIDK C24H17N5O2S CLOGP 4.33 Structure BIDM C29H23N5O2 CLOGP 4.87 Structure BIDN C29H23N5O2 CLOGP 3.11 Structure BIDO C30H29N5O2 CLOGP 5.77	Or Or or	C ₂₆ H ₂₅ N ₅ O ₂	0,000	C ₂₅ H ₂₃ N ₅ O ₂
Structure BIDK $C_{24}H_{17}N_{5}O_{2}S$ C_{10GP} $C_{29}H_{23}N_{5}O_{2}$ C_{10GP} $C_{29}H_{23}N_{5}O_{2}$ C_{10GP} $C_{29}H_{23}N_{5}O_{2}$ C_{10GP} $C_{29}H_{23}N_{5}O_{2}$ C_{10GP} $C_{21}H_{17}N_{5}O_{2}S$ C_{10GP} $C_{27}H_{27}N_{5}O_{2}S$ C_{10GP}				·
Structure		<u></u>		
Structure	Structure	BIDK	Structure	BIDL
Structure	0,000	C ₂₄ H ₁₇ N ₅ O ₂ S	Or Orrive	C ₂₄ H ₁₇ N ₅ O ₂ S
Structure BIDM C29H23N5O2 CLOGP 4.87 Structure BIDO C30H29N5O2 CLOGP 5.77 Structure BIDO C27H27N5O2 CLOGP 5.77	***			
Structure BIDO C29H23N5O2 CLOGP 3.11		4.33		4.33
Structure BIDO Canhapana Canhapana	Structure	BIDM	Structure	BIDN
Structure BIDO Structure BIDP C ₂₇ H ₂₇ N ₅ O ₂ CLOGP 5.77 CLOGP 5.70		C ₂₉ H ₂₃ N ₅ O ₂	Or Or	° C ₂₁ H ₁₇ N ₅ O ₂
Structure BIDO C ₃₀ H ₂₉ N ₅ O ₂ CLOGP 5.77 Structure BIDP C ₂₇ H ₂₇ N ₅ O ₂ CLOGP 5.70		CLOGP	N-1	CLOGP
C ₃₀ H ₂₉ N ₅ O ₂ CLOGP 5.77		4.87		3.11
C ₃₀ H ₂₉ N ₅ O ₂ CLOGP 5.77	[a		Structure	<u></u>
CLOGP CLOGP 5.77	Structure	BIDO	N	BIDP
5.77		C ₃₀ H ₂₉ N ₅ O ₂	Or Or Direct	C ₂₇ H ₂₇ N ₅ O ₂
		1		İ
Structure BIDQ C27H25N5O2 CLOGP Structure BIDR C27H23N5O2 CLOGP		5.77		5.70
C ₂₇ H ₂₅ N ₅ O ₂ CLOGP CLOGP	Structure	BIDQ	Structure .	BIDR
CLOGP	1 3	C27H25N5O2		C ₂₇ H ₂₃ N ₅ O ₂
	, oit	<u>_</u> }		CLOGP

Structure	BIEA
Drango	C ₃₀ H ₂₆ N ₄ O ₅
	CLOGP
	4.82

Structure	BIEB
1.3.0. 10°	C ₃₀ H ₂₅ CIN ₄ O ₅
1, , , , ,	CLOGP
	5.59

Structure	BIEC
Dinord.	C ₃₁ H ₂₈ N ₄ O ₆
1	CLOGP
	4.93

Structure	BIED
Branco	C ₂₉ H ₂₅ N ₅ O ₅
	CLOGP
	3.63

Structure	BIEE
	CHN-O-
in order	C ₃₃ H ₃₂ N ₄ O ₈
i i	CLOGP
	4.17

Structure	BIEF
Dran i	C ₃₀ H ₂₄ Cl ₂ N ₄ O ₅
I DAG.	CLOGP
	6.32

Structure	BIEG
dimora:	C ₃₀ H ₂₄ Cl ₂ N ₄ O ₅
1	CLOGP
	4.66

Structure	BIEH
diam's	C ₃₀ H ₂₄ Cl ₂ N ₄ O ₅
1	CLOGP
	5.49

Structure	BIEI
ourson's	C ₃₀ H ₃₂ N ₄ O ₅
1	CLOGP
	5.36

Structure	BIEJ
· in the	C ₂₉ H ₃₀ N ₄ O ₅
1 , , , , , ,	CLOGP
	4.80

Structure	BIEK
Drango	C ₂₈ H ₂₄ N ₄ O ₅ S
	CLOGP
	4.55

Structure	вієм	Structure	BIEN
مرائد م المرائد	C ₃₃ H ₃₀ N ₄ O ₅	· D. O	C ₂₅ H ₂₄ N ₄ O ₅
	CLOGP		CLOGP
	5.09		3,33
Structure	BIEO	Structure	BIEP
	C ₃₄ H ₃₆ N ₄ O ₅	Diano	C ₃₁ H ₃₄ N ₄ O ₅
Diring !	CLOGP	1, ,	CLOGP
	5.99		5.92
	·		
Structure	BIEQ	Structure	BIER
722	C ₃₁ H ₃₂ N ₄ O ₅	ipioidi	C ₃₁ H ₃₀ N ₄ O ₅
1201	CLOGP	177	CLOGP
' (5.11	,	4.63
	1	Structure	
Structure	BIFA	a.	BIFB
Dra co	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂	Drawio.	C ₂₇ H ₁₇ Cl ₃ N ₄ O ₂
	1 .		
la grand	CLOGP		CLOGP
	L		CLOGP 7.78
	CLOGP		1 1
Structure	CLOGP	Structure	1 1
Structure	CLOGP 7.00	Structure	7.78
Structure	7.00		7.78 BIFD C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂ CLOGP
Structure	7.00 BIFC C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃		8IFD C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂
المن من الم	T.00 BIFC C28H20Cl2N4O3 CLOGP	المن المالية	7.78 BIFD C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂ CLOGP 5.82
Structure Structure	T.00 BIFC C28H20Cl2N4O3 CLOGP		7.78 BIFD C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂ CLOGP
المن من من	T.00 BIFC C28H20Cl2N4O3 CLOGP 7.12	المن المالية	7.78 BIFD C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂ CLOGP 5.82
منوره	BIFC C28H20Cl2N4O3 CLOGP 7.12 BIFE	المن المالية	7.78 BIFD C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂ CLOGP 5.82

Structure	BIFG	Structure	BIFH
13	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂	in in	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂
	CLOGP		CLOGP
	6.85		7.68
Structure	BIFI	Structure	BIFJ
D	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂	D'0-0	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₂
	CLOGP		CLOGP
	7.54		6.99
Structure	· · · · · · · · · · · · · · · · · · ·	Structure]
o,	BIFK	1	BIFL
Drango.	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S	Diago.	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S
	CLOGP	*	CLOGP 6.74
	6.74		0.74
Structure	BIFM	Structure	BIFN
			C ₂₂ H ₁₆ Cl ₂ N ₄ O ₂
	C ₃₀ H ₂₂ Cl ₂ N ₄ O ₂		CLOGP
	7.28		5.51
Structure	BIFO	Structure	BIFP
	C31H28Cl2N4O2	Drn :0	C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂
Di My C	CLOGP		CLOGP
	8.17		8.10
lott		Structure	
Structure	BIFQ	.A	BIFR
्र स्ट	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₂	1	C28H22CI2N4O2
~~~	20. 24 - 2 - 4 - 2		1 1
Structure	CLOGP 7.30	Structure	CLOGP 6.82

	<del>,</del> .		<del></del>
Structure	BIGA	Structure	BIGB
Min on	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂	12°	C ₂₇ H ₁₇ Cl ₃ N ₄ O ₂
Le Miller		121000	
	CLOGP		CLOGP 6.12
	5.34	<u></u>	6.12
Structure	BIGC	Structure	BIGD
of many of the	C. H. CiaN.Oa	M. on	CaeHazClaNsOa
Le China	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃	Le Carrie	C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂
	CLOGP		CLOGP
	5.46		4.16
Structure	BIGE	Structure	BIGF
10°00 : "		Time :	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂
11,0000	C ₃₀ H ₂₄ Cl ₂ N ₄ O ₅	1,000	
1	CLOGP	0 0	CLOGP
	4.69		6.85
			<del></del>
Structure	BIGG	Structure	BIGH
10° m	C - H - C - N - O -	Time in	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂
I LI CONTO	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂	Les of the	
	CLOGP	·	CLOGP 6.02
	5.19		6.02
-			
Structure	BIGI	Structure	BIGJ
	)   CH-, CI-N-C-	Ich	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₂
I TO THE TO THE	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂	Le plant	
	CLOGP		CLOGP
	5.88		5.33
			<u></u>
Structure	BIGK	Structure	BIGL
	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂		C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂
The state of the s	s  s	I'M MIN	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S
	CLOGP		CLOGP
	5.08	<u> </u>	5.08

BIGM	Structure	BIGN
C ₃₀ H ₂₂ Cl ₂ N ₄ O ₂	Gronn.	C ₂₂ H ₁₆ Cl ₂ N ₄ O ₂
CLOGP		CLOGP 3.85
5.62		3.63
BIGO	Structure	BIGP
C ₃₁ H ₂₈ Cl ₂ N ₄ O ₂	Granio	C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂
CLOGP	<b>"-</b>	CLOGP
6.51		6.44
BIGQ	Structure	BIGR
C ₂₈ H ₂₄ Cl ₂ N ₄ O ₂	منت	C ₂₈ H ₂₂ Cl ₂ N ₄ O ₂
CLOGP	di.	CLOGP
5.64		5.16
ВІНА	Structure	вінв
C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂	Promo.	C ₂₇ H ₁₇ Cl ₃ N ₄ O ₂
CLOGP		CLOGP 6.95
6.17		0.93
вінс	Structure	BIHD
C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃	Organo P	C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂
CLOGP		CLOGP
6.29		4.99
BIHE	Structure	BIHF
BIHE C ₃₀ H ₂₄ Cl ₂ N ₄ O ₅	Structure	BIHF C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂
	C30H22CI2N4O2 CLOGP 5.62  BIGO  C31H28CI2N4O2 CLOGP 6.51  BIGQ  C28H24CI2N4O2 CLOGP 5.64  BIHA  C27H18CI2N4O2 CLOGP 6.17  BIHC  C28H20CI2N4O3	BIGM

Structure	вінс
Cinory	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂
	CLOGP
	6.02
Structure	віні

Structure	ВІНН
Second.	C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂
	CLOGP
	6.85

Structure	віні
Of Other	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂
	CLOGP
	6.71

Structure	BIHJ
Of TOTO	C ₂₆ H ₂₂ Ci ₂ N ₄ O ₂
	CLOGP
	6.16

Structure	вінк
010000	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S
	CLOGP
·	5.91

Structure	BIHL
Of Office	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S
	CLOGP
	5.91

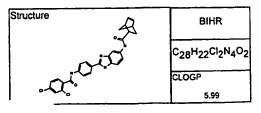
Structure	вінм
منی ب	C ₃₀ H ₂₂ Cl ₂ N ₄ O ₂
	CLOGP
	6.45

Structure	BIHN
Chickey.	C ₂₂ H ₁₆ Cl ₂ N ₄ O ₂
	CLOGP
	4.68

Structure	ВІНО
	C31H28Cl2N4O2
	CLOGP
	7.34

Structure	BIHP
Oin oin	C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂
	CLOGP
	7.27

Structure	A	ВІНО
_	155	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₂
ا من	•	CLOGP
۰۰۰۰		6.47

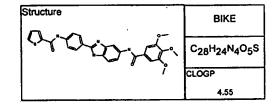


Structure	BIKA
0,000	C ₂₅ H ₁₈ N ₄ O ₂ S
	CLOGP
	5.20

Structure	ВІКВ
of Oirio.	C ₂₅ H ₁₇ CIN ₄ O ₂ S
	CLOGP
	5.98

Structure	вікс
oranio.	C ₂₆ H ₂₀ N ₄ O ₃ S
	CLOGP
	5.32

Structure	BIKD
04.00.00	C ₂₄ H ₁₇ N ₅ O ₂ S
	CLOGP
	4.02



Structure	BIKF
arara,	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S
	CLOGP
	6.71

Structure	BIKG
Ciropo Po	С ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ s
	CLOGP
	5.05

Structure	ВІКН
، خزیری می این این این این این این این این این ای	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S
	CLOGP
	5.88

Structure	ВІКІ
Of any	C ₂₅ H ₂₄ N ₄ O ₂ S
	CLOGP
	5.74

Structure	BIKJ
010110	C ₂₄ H ₂₂ N ₄ O ₂ S
	CLOGP
	5.19

Structure	вікк
010110	C ₂₃ H ₁₆ N ₄ O ₂ S ₂
	CLOGP
	4 04

Structure	<del></del>	Structure	1
Structure	ВІКМ		BIKN
	C28H22N4O2S	STATE YOU	C ₂₀ H ₁₆ N ₄ O ₂ S
	CLOGP		CLOGP
	5.48		3.71
	1	<u> </u>	
Structure	віко	Structure	BIKP
	·		
	C ₂₉ H ₂₈ N ₄ O ₂ S	C. L. C.	C ₂₆ H ₂₆ N ₄ O ₂ S
	CLOGP		CLOGP .
	6.37		6.30
			<del></del>
Structure	віко	Structure	BIKR
3	C ₂₆ H ₂₄ N ₄ O ₂ S	<b>5</b>	C ₂₆ H ₂₂ N ₄ O ₂ S
\ \tag{in}		نگزنی.	CLOGP
م ا	CLOGP 5.50	Cri.	5.02
			<u></u>
Structure	BILA	Structure	BILB
	8125		
1 Charles	C ₂₅ H ₁₈ N ₄ O ₂ S	1 of the said	C ₂₅ H ₁₇ CIN ₄ O ₂ S
***	CLOGP		CLOGP
	5.20		5.98
Structure	BILC	Structure	BILD
	6 C ₂₆ H ₂₀ N ₄ O ₃ S	D	C ₂₄ H ₁₇ N ₅ O ₂ S
1 de la como			
	CLOGP		CLOGP 4.02
<u></u>	5.32		7.02
Structure		Structure	
A	BILE		BILF
14 Direct	C ₂₈ H ₂₄ N ₄ O ₅ S	TOWN A	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂ S
	CLOGP		CLOGP
	4.55		6.71

5.02

Structure	BILG	Structure	BILH
Din in	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂	2000	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₂
	CLOGP		S CLOGP
	5.05	•	5.88
<u> </u>			· · · · · · · · · · · · · · · · · · ·
Structure	BILI	Structure	BILJ
04000	C ₂₅ H ₂₄ N ₄ O ₂ S	0,000	C ₂₄ H ₂₂ N ₄ O ₂ S
"-	CLOGP		CLOGP
	5.74		5.19
	·		, — — — — — — — — — — — — — — — — — — —
Structure	BILK	Structure	BILL
0000	C ₂₃ H ₁₆ N ₄ O ₂ S ₂	0,000	C ₂₃ H ₁₆ N ₄ O ₂ S ₂
	CLOGP		CLOGP
	4.94		4.94
Structure	BILM	Structure	BILN
	C ₂₈ H ₂₂ N ₄ O ₂ S		C ₂₀ H ₁₆ N ₄ O ₂ S
	CLOGP	***	CLOGP
	5.48		3.71
			·
Structure o	BILO	Structure	BILP
	C ₂₉ H ₂₈ N ₄ O ₂ S	00000	C ₂₆ H ₂₆ N ₄ O ₂ S
	CLOGP		CLOGP
	6.37		6.30
Structure	BILQ	Structure	BILR
. Sinctione	C ₂₆ H ₂₄ N ₄ O ₂ S		C ₂₆ H ₂₂ N ₄ O ₂ S
.04.50	CLOGP		CLOGP

Structure	BIJG
Quano po	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₂
	CLOGP
	5.29

Structure	ВІЈН
0,000	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₂
	CLOGP
	6.12

Structure	BIIA
0,000	C ₂₇ H ₂₆ N ₄ O ₂
	CLOGP
	6.01

Structure	BIIB
de diviso.	C ₂₇ H ₂₅ CIN ₄ O ₂
	CLOGP
	6.78

Structure	BIIC
000000	C ₂₈ H ₂₈ N ₄ O ₃
	CLOGP
	6.12

Structure	BIID
0,000	C ₂₆ H ₂₅ N ₅ O ₂
	CLOGP
	4.82

Structure	BIIE
araway.	C ₃₀ H ₃₂ N ₄ O ₅
	CLOGP
	5.36

Structure	BIIF
Or Orriginal	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂
	CLOGP
·	7.51

Structure	BIIG
0,000	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂
	CLOGP
	5.85

Structure	BIIK
0,0000	C ₂₅ H ₂₄ N ₄ O ₂ S
"-	CLOGP
	5.74

Structure	BIIL
0,0000	C ₂₅ H ₂₄ N ₄ O ₂ S
	CLOGP
	5.74

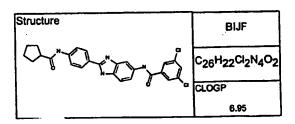
Structure	BIJA
0,000	C ₂₆ H ₂₄ N ₄ O ₂
	CLOGP
	5.45

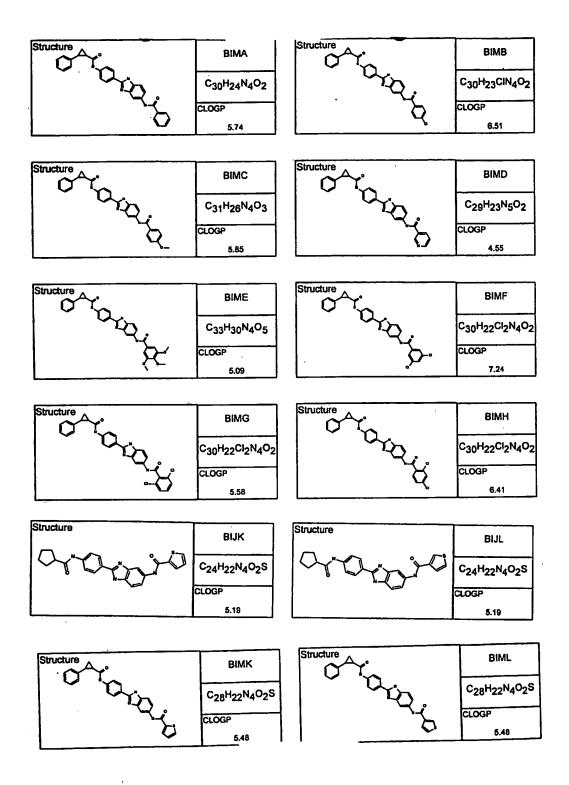
Structure	віјв
0,0000	C ₂₆ H ₂₃ CIN ₄ O ₂
	CLOGP
	6.22

Structure	BIJC
granio	C ₂₇ H ₂₆ N ₄ O ₃
	CLOGP
	5.56

Structure	BIJD
00000	C ₂₅ H ₂₃ N ₅ O ₂
	CLOGP
	4.26

Structure	BIJE
grown.	C ₂₉ H ₃₀ N ₄ O ₅
	CLOGP
	4.80





Structure	BINK
المريات،	C ₂₀ H ₁₆ N ₄ O ₂ S
	CLOGP
	3.71

Structure	BINL
200	C ₂₀ H ₁₆ N ₄ O ₂ S
	CLOGP
	3.71

Structure	BING
Q'	C ₂₂ H ₁₆ Cl ₂ N ₄ O ₂
	CLOGP
	3.82

Structure	BINH
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	C ₂₂ H ₁₆ Cl ₂ N ₄ O ₂
*	CLOGP
	4.65

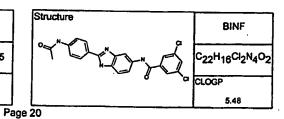
Structure	BINA
	C ₂₂ H ₁₈ N ₄ O ₂
	CLOGP
	3.98

Structure	BINB
.LO(2)0.	C22H17CIN4O2
	CLOGP
	4.75

Structure	BINC
- CO () CO	C ₂₃ H ₂₀ N ₄ O ₃
	CLOGP
	4.09

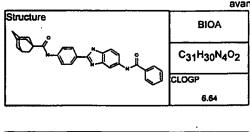
Structure	BIND
01.01.01.0	C ₂₁ H ₁₇ N ₅ O ₂
	CLOGP
·	2.79

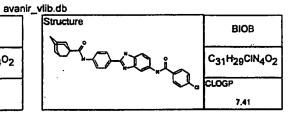
Structure	BINE
1 voya	C ₂₅ H ₂₄ N ₄ O ₅
7	CLOGP
	3.33
•	



Structure	вюк
D. Chilli	C ₂₉ H ₂₈ N ₄ O ₂ S
	CLOGP
	6.37

Structure	BIOL
P. CAN:	C ₂₉ H ₂₈ N ₄ O ₂ S
	CLOGP
	6.37





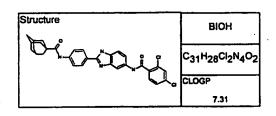
Structure	BIOC
Din.	CaaHaaNaOa
	C ₃₂ H ₃₂ N ₄ O ₃
	CLOGP
	6.75

Structure	BIOD
Di-O-Dia	C ₃₀ H ₂₉ N ₅ O ₂
	CLOGP
	5.45

Structure	BIOE
-Cilian	C ₃₄ H ₃₆ N ₄ O ₅
	CLOGP
	5.99

Structure	BIOF
0-0-00in	C ₃₁ H ₂₈ Cl ₂ N ₄ O ₂
7	CLOGP
	8.14

Structure	BIOG
D'O'ILLI	C ₃₁ H ₂₈ Cl ₂ N ₄ O ₂
	CLOGP
	6.48



Structure	BIPG
Oranio	C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂
	CLOGP
	6.41

Structure	вірн
00000	C ₂₈ H ₂₆ Cl ₂ N ₄ O ₂
	CLOGP
	7.24

Structure	вірк
0,0000	C ₂₆ H ₂₆ N ₄ O ₂ S
	CLOGP
	6.30

Structure	BIPL
0,0000	C ₂₆ H ₂₆ N ₄ O ₂ S
H ————————————————————————————————————	CLOGP
	6.30

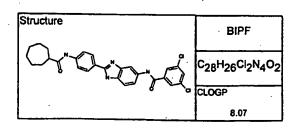
Structure	BIPA
0,000	C ₂₈ H ₂₈ N ₄ O ₂
	CLOGP
	6.57

Structure	BIPB
0,0000	C ₂₈ H ₂₇ CIN ₄ O ₂
	CLOGP
	7.34

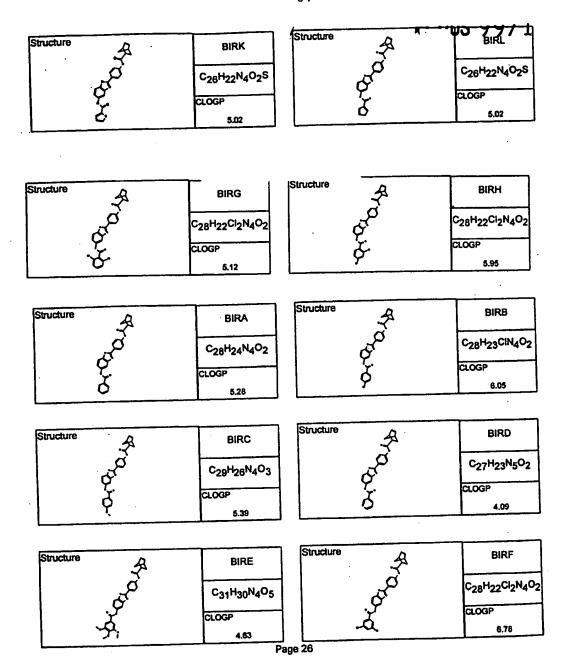
Structure	BIPC
000000	C ₂₉ H ₃₀ N ₄ O ₃
	CLOGP
	6.68

Structure	BIPD
Orogania	C ₂₇ H ₂₇ N ₅ O ₂
	CLOGP
	5.38

Structure	BIPE
10.00	
A COLOR	C ₃₁ H ₃₄ N ₄ O ₅
, , ,	CLOGP
	5.92



	8IQB 28 ^H 25 ^{CIN} 4 ^O 2 OGP 6.54
	OGP
	0.54
Structure & BIQC Structure	
Structure BIQC Structure	
1 2 1 5	BIQD
C ₂₉ H ₂₈ N ₄ O ₃	C ₂₇ H ₂₅ N ₅ O ₂
CLOGP C	.OGP
6.88	4.57
0.00	
Structure BIQE C ₃₁ H ₃₂ N ₄ O ₅ CLOGP 6.11 Structure CC	BIQF
C ₃₁ H ₃₂ N ₄ O ₅ C ₂	28H24Cl2N4O2
CLOGP Y	.OGP
	7.27
5.11	
Structure BIQG Structure	віон
Structure BIQG C ₂₈ H ₂₄ Cl ₂ N ₄ O ₂ CLOGP 5.61 Structure C ₂₈ H ₂₄ Cl ₂ N ₄ O ₂ C ₂₈ H ₂₄ Cl ₂ N ₄ O ₂ C ₃ ClogP	28H24Cl2N4O2
CLOGP CL	LOGP
5.61	6.44
0	
Structure A BIQK Structure A	BIQL
$ C_{26}H_{24}N_4O_2S C_{26}H_{24}N_4O_2S $	26H24N4O2S
C ₂₆ H ₂₄ N ₄ O ₂ S	26H24N4O2S
	0GP



- 4. The pharmaceutical composition of any of Claims 1-3 for use in the treatment of a disease condition associated with excess IgE.
- 5. The pharmaceutical composition of Claim 4, further comprising at least one additional ingredient which is active in reducing at least one symptom associated with the disease condition associated with excess IgE.
- 6. The pharmaceutical composition of Claim 5, wherein said at least one additional ingredient is selected from the group consisting of a short-acting β_2 -adrenergic agonist, a long-acting β_2 -adrenergic agonist, an antihistamine, a phosphodiesterase inhibitor, an anticholinergic agent, a corticosteroid, an inflammatory mediator release inhibitor and a leukotriene receptor antagonist.
- 7. Use of the pharmaceutical composition of any one of Claims 1-3 in the preparation of a medicament for treatment of a disease condition associated with excess IgE.

INTERNATIONAL SEARCH REPORT

Inte onal Application No PCT/US 99/11322

A. CLASS	FICATION OF SUBJECT MATTER				
IPC 6	A61K31/415				
According t	o International Patent Classification (IPC) or to both national classific	cation and IPC	•		
B. FIELDS	SEARCHED				
Minimum do	ocumentation searched (classification system followed by classification	ion symbols)			
IPC 6	A61K				
Documenta	tion searched other than minimum documentation to the extent that	such documents are included in the fields se	arched		
Electronic d	ata base consulted during the international search (name of data be	see and where practical search terms used	`		
		and, whore planting, couldn't child acce	,		
	,				
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT				
Category *	Citation of document, with indication, where appropriate, of the re	levant passages	Relevant to claim No.		
χ	EP 0 719 765 A (MITSUI TOATSU CH	FMICALS)	1-4		
	3 July 1996 (1996-07-03)		• 7		
	page 30				
	page 31		·		
	page 38				
	page 39 page 49				
	page 50; claim 1; examples 43,88	1100 2100			
		,1100,2100			
ĺ					
ļ					
ļ		· -			
Furth	er documents are listed in the continuation of box C.	Patent family members are listed in	n annex.		
* Special cat	egories of cited documents :				
		"T" later document published after the inter or priority date and not in conflict with t			
conside	"A" document defining the general state of the art which is not considered to be of particular relevance or priority date and not in conflict with the application but citizent to understand the principle or theory underlying the invention				
"E" earlier document but published on or after the international filling date "X" document of particular relevance; the claimed invention					
"L' document which may throw doubts on priority, claim(a) or					
CILETION	s cited to establish the publication date of another or other special reason (as specified)	"Y" document of particular relevance; the cla cannot be considered to involve an invo	aimed invention		
"O" docume other m	nt referring to an oral disclosure, use, exhibition or seans	document is combined with one or mor ments, such combination being obvious	e other such docu-		
"P" documer	nt published prior to the international filing date but	in the art.			
tater (n	an the priority date claimed	*&* document member of the same patent for	 		
Sale of the B	ctual completion of the international search	Date of mailing of the international sear	rch report		
1	October 1999	11/10/1999			
Name and m	ailing address of the ISA	Authorized officer			
	European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk				
	Tel. (+31-70) 340-2040, Tx. 31 651 epo nt, Fax: (+31-70) 340-3016	Orviz Diaz, P			

INTERNATIONAL SEARCH REPORT

smational application No.

PCT/US 99/11322

Box I	Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This Inte	emational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1.	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. X	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: See FURTHER INFORMATION SHEET PCT/ISA/210
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)
This Inte	mational Searching Authority found multiple inventions in this international application, as follows:
1	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
	
4.	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark (on Protest The additional search fees were accompanied by the applicant's protest.
	No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 /11322

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The substituents in the general formula of claim 1 are not clearly defined, contrary to Art. 6 PCT. The expressions "the like" or "substituted aryl", for example, encompass an extremely large number of possiblities, which makes impossible to carry out a complete search.

Furthermore, most of the specific R1 and R2 substituents mentioned in claim 2 are not covered by claim 1 and some of the compounds mentioned in claim 3 have a pyridine ring or a thiophene ring, which are not mentioned as possible substituents in claim 1.

In view of this the search had to be limited to the general structural characteristics of the formula in claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

L			ARCH REPORT	ibers	Into Pi	 Application No 39/11322
Pa cited	atent document I in search repor	t	Publication date	F	Patent family member(s)	Publication date
EP 	0719765 	Α	03-07-1996	JP US	8231514 5821258	10-09-1996 13-10-1998
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			-			